



Original Article

Sleep disorders increase the risk of osteoporosis: a nationwide population-based cohort study



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ABSTRACT

Background: This study evaluated the relationship between sleep disorders (SDs) and osteoporosis risk in Taiwan.

Methods: From the Taiwan National Health Insurance data, we identified 44,690 newly diagnosed SD patients (846 with apnea and 43,844 without) from 1998 to 2001 and 89,380 comparisons without SD in the same period frequency matched by sex, age and diagnosis year. Incident osteoporosis was measured by the end of 2010.

Result: Patients with apnea-SD and nonapnea SD exhibited a higher osteoporosis incidence rate than did the comparisons (9.97 and 13.3 vs. 6.77 per 1000 person-years, respectively). The Cox method estimated adjusted hazard ratio (HR) of osteoporosis was 2.98 (95% confidence interval [CI] = 2.36–3.74) in apnea-SD patients, compared with 2.76 (95% CI = 2.64–2.88) in nonapnea-SD patients after controlling for sex, age, comorbidities, and treatment. Greater HRs of osteoporosis were observed for female patients (4.00, 95% CI = 3.72–4.29) and those aged >64 years (42.0, 95% CI = 33.5–52.7) in the apnea SD sub-cohort. Apnea SD was associated with the highest risk of osteoporosis without fracture compared with both the nonapnea SD sub-cohort and comparisons.

Conclusion: Patients with sleep disorders have an elevated risk of osteoporosis, especially for women and the elderly.

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Author contributions

Chia-Ming Yen and Chia-Hung Kao conceived and designed the experiments. Chia-Ming Yen, Cheng-Li Lin, and Chia-Hung Kao performed the experiments. Chia-Ming Yen, Cheng-Li Lin, and Chia-Hung Kao analyzed the data. Chia-Hung Kao contributed the reagents/materials/analysis tools. All authors wrote and approved the manuscript.

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1. Introduction

At least 10% of the U.S. population suffers from the clinically significant sleep disorder that is of importance to public health [1]. An earlier study in Los Angeles suggested that approximately 33% of the population suffers from symptoms of insomnia [2]. Sleep disturbances are often associated with multifaceted severe consequences including psychiatric symptoms and disorders [3]. In addition to mental disease, patients with sleep disorder (SD) have been associated with the risk of developing various physical diseases such as cardiovascular disease, type 2 diabetes mellitus, obesity, cancer, depression, and total mortality [4–7]. Poor sleep has been related to proinflammatory cytokine production and immunosuppression [8]. Patients with SD have been found to have increased risk of liver cancer and breast cancer [5].

Studies have also investigated the association between SD, bone mineral density, and osteoporosis with conflicting results. Patients with osteoporosis are characterized with a reduction in bone mass, disruption of bone microarchitecture, and skeletal fragility [6]. Osteoporosis is a multifactorial chronic systemic disease occurring mainly in the elderly [7].

Intermittent hypoxia mimicking obstructive sleep apnea in animal study could not modify bone mineral density in mice [8]. One study found that the elderly patients with obstructive sleep apnea have higher femoral and spinal bone mineral density than participants without the disorder [9]. Another study by Tomiyama et al. found that patients with obstructive sleep apnea had a higher risk of developing abnormal bone metabolism [10].

Restless legs syndrome (RLS), another sleep disorder, is the fourth most common cause of insomnia. Almost 50–85% of RLS patients have experienced of insomnia [11]. A Norwegian study using the prospective population-based data found osteoporosis co-occurring in insomnia patients with an odds ratio of 1.52 (95% confidence interval: 1.14–2.01) [12].

The severity of sleep-related diseases may differ among ethnic groups. The relationship between sleep disorders and bone marrow density may be variable among populations. To determine whether sleep disorders induce osteoporosis in the population of Taiwan, we analyzed data obtained from the National Health Insurance Research Database (NHIRD).

2. Methods

2.1. Data sources

The present study was a population-based retrospective cohort study using the NHIRD, which has been described in detail in a previous study [5]. In brief, the National Health Research Institute (NHRI) of Taiwan has maintained a large computerized administrative database assembled from the National Health Insurance (NHI) medical records, including data on outpatient visits, hospital admissions, prescriptions, and disease status for all insurants. The NHI program covers 99.9% of the 23.74 million people residing in Taiwan. The NHRI encrypts patients' personal information for privacy protection and provides researchers with anonymous identification numbers associated with relevant claim information including patient sex, date of birth, registry of medical services, and medication prescriptions. Patient consent is not required for accessing the NHIRD. This study was approved by an ethical review of the China Medical University in Central Taiwan (CMU-REC-101-012).

The data used in this study were obtained from a sub-dataset of the NHIRD, which comprised one million randomly sampled beneficiaries enrolled in the NHI program; medical records from 1996 to 2010 of these individuals were obtained. The diagnoses and procedures are coded in the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) format.

2.2. Study patients

Our SD cohort included individuals with sleep apnea syndrome (apnea SD) and nonapnea sleep disorder (nonapnea SD) newly diagnosed from 1998 to 2001. Patients with non-apnea sleep disorders included unspecified insomnia, sleep disturbance, and others. Only patients with three diagnoses were selected in the period from 1998 to 2001. Diagnosis was usually made from medical and family histories, and by polysomnogram. Patients were excluded if they had an osteoporosis history or were younger than 20 years. The date of the first diagnosis of SD was used as the index date for estimating follow-up years. A total of 846 patients with apnea SD and 43,844 patients with nonapnea SD were identified for this study. For each SD patient, we randomly selected two patients without SD as comparisons from the same data file under the same exclusion criteria, frequency matched by sex, age, and index date. Overall, 89,380 persons were selected for the comparison cohort.

2.3. Outcome measurement and comorbidities

Each study patient was followed up until a diagnosis of osteoporosis was made, until the end of 2010, or until the patient was censored for loss to follow-up, death, withdrawal from the database, whichever occurred first. The diagnosis of osteoporosis is generally based on the bone mineral density exam. Subjects with diagnoses of osteoporosis were considered as incident cases.

We also incorporated inpatient and outpatient diagnostic records to ascertain the baseline comorbidities including diabetes, hypertension, hyperlipidemia, chronic kidney disease, stroke, chronic obstructive pulmonary disease, cancer, anxiety, and depression [4,5,13–19]. Since the NHIRD did not include complete data on obesity (one of the study limitations), we used the co-morbidities of Triple H (hypertension, hyperlipidemia, hyperglycemia) to replace the influence of obesity because Triple H and obesity are highly correlated and both closely related to sleep disorders and osteoporosis. We also considered benzodiazepine and zolpidem as anti-SD treatments for SD.

2.4. Statistical analysis

Data analysis involved comparing distributions of age, sex, and comorbidities between the SD cohort and comparison cohort using the Chi-square test. We calculated the incidence density of osteoporosis by each variable. The SD-to-comparisons incidence rate ratio (IRR) of osteoporosis and a 95% confidence interval (CI) by variables were calculated using Poisson regression. A multivariable Cox proportional-hazards regression analysis was used to determine the effects of SD on the risks of osteoporosis, as indicated by a hazard ratio (HR) with a 95% CI. The multivariable models were simultaneously adjusted for establishing the demographic characteristics, baseline comorbidities, and treatment. For estimating the cumulative incidence in non-SD patients and SD patients with a subtype of SD, we used the Kaplan–Meier method, with significance based on the log-rank test.

All analyses were performed using SAS statistical software (version 9.2; SAS Institute, Inc., Cary, NC), and the results were considered statistically significant when 2-tailed *P* values were less than 0.05.

3. Results

A total of 44,690 cases of SD (846 cases of apnea SD and 43,844 cases of nonapnea SD) and 89,380 comparisons were identified from the NHIRD for the defined period of interest. Among the SD cases and comparisons, 49.1% were 40–64 years of age and 60.7% were women (Table 1). The SD cohort was more likely to have diabetes

Table 1

Comparison of demographics and comorbidity between SD patients and controls.

	Sleep disorder								P-value
	Apnea SD (N = 846)		Non-apnea SD (N = 43844)		Total (N = 44,690)		Control (N = 89,380)		
	n	%	n	%	n	%	n	%	
Age, year									
≤39	255	30.1	11,651	26.6	11,906	26.6	23,818	26.7	0.99
40–64	454	53.7	21,491	49.0	21,945	49.1	43,884	49.1	
>64	137	16.2	10,702	24.4	10,839	24.3	21,678	24.3	
Mean (SD)#	48.9	14.5	51.7	16.1	51.6	16.0	51.4	16.2	0.03
Sex									
Female	290	34.3	26,852	61.2	27,142	60.7	54,284	60.7	0.99
Male	556	65.7	16,992	38.8	17,548	39.3	35,096	39.3	
Comorbidity									
Diabetes	80	9.46	4,852	11.1	4,932	11.0	6,498	7.27	<0.0001
Hypertension	327	38.7	16,666	38.0	16,993	38.0	19,851	22.2	<0.0001
Hyperlipidemia	215	25.4	8,530	19.5	8,745	19.6	8,347	9.34	<0.0001
CKD	88	10.4	3,832	8.74	3,920	8.77	3,811	4.26	<0.0001
Stroke	23	2.72	1,613	3.68	1,636	3.66	2,291	2.56	<0.0001
COPD	330	39.0	15,435	35.2	15,765	35.3	16,028	17.9	<0.0001
Cancer	13	1.54	968	2.21	981	2.20	14,80	1.66	<0.0001
Anxiety	40	4.73	2,341	5.34	2,381	5.33	460	0.51	<0.0001
Depression	58	6.86	2,584	6.51	2,912	6.52	502	0.56	<0.0001
Treatment									
Benzodiazepine	804	95.0	42,897	97.8	43,701	98.0	62,840	70.3	<0.0001
Zolpidem	501	59.2	27,317	62.3	27,818	62.3	8,033	8.99	<0.0001

Chi-square test compared to total SD; #;T-test.

Diseases in this study were identified using codes of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). They were: apnea sleep disorder (apnea SD) (780.51, 780.53 and 780.57); nonapnea sleep disorder (nonapnea SD) including patients with unspecified insomnia (ICD-9-CM codes 780.52), sleep disturbance (ICD-9-CM codes 780.5), and others (ICD-9-CM codes 307.4, 780.50, 780.54–780.56, 780.58–780.59); osteoporosis (ICD-9-CM 733.0 and 733.1); diabetes (ICD-9-CM 250); hypertension (ICD-9-CM 401–405); hyperlipidemia (ICD-9-CM 272); chronic kidney disease (CKD) (ICD-9-CM 575); stroke (ICD-9-CM 430–438); chronic obstructive pulmonary disease (COPD) (ICD-9-CM 490–496); cancer (ICD-9-CM 140–208), anxiety (ICD-9-CM 300.00) and depression (ICD-9-CM 296.2–296.3, 300.4).

(11.0% vs. 7.27%, $P < 0.0001$), hypertension (38.0% vs. 22.2%, $P < 0.0001$), hyperlipidemia (19.6% vs. 9.34%, $P < 0.0001$), chronic kidney disease (8.77% vs. 4.26%, $P < 0.0001$), stroke (3.66% vs. 2.56%, $P < 0.0001$), chronic obstructive pulmonary disease (35.3% vs. 17.9%, $P < 0.0001$), cancer (2.20% vs. 1.79%, $P < 0.0001$), anxiety (5.33% vs. 0.51%, $P < 0.0001$) and depression (6.52% vs. 0.56%, $P < 0.0001$). Patients in the SD cohort were more likely to use anti-SD medication(s) than those in the non-SD cohort (98.0% vs. 70.3%, $P < 0.0001$ for benzodiazepine, 62.3% vs. 8.99%, $P < 0.0001$ for zolpidem).

Fig. 1 shows the Kaplan–Meier method measured cumulative proportional incidence of osteoporosis by study cohort. The risk of osteoporosis was 6% higher in SD patients than in comparisons, particularly in SD patients with apnea (7% higher) (log-rank $P < 0.001$).

Table 2 lists the osteoporosis incidence densities for the study cohorts and shows apnea-SD-to-comparisons and nonapnea-SD-to-comparisons HRs controlling for covariates. Overall, a higher osteoporosis incidence was determined in both the apnea SD cohort and nonapnea SD cohort than in the non-SD controls (9.97 and 13.3 vs. 6.77 per 1000 person-years, respectively). Compared to the non-SD cohort, the adjusted HRs of osteoporosis were 2.98 (95% CI = 2.36–3.74) for the apnea SD cohort, and 2.76 (95% CI = 2.64–2.88) for the nonapnea SD cohort.

In patients with apnea SD, female patients had a significantly increased risk of osteoporosis with an adjusted HR of 4.00 (95% CI = 3.72–4.29). The age-specific HR increased with age with the highest HR of 42.0 (95% CI = 33.5–52.7) in patients aged >64 years. Compared with patients without comorbidities, the HR of osteoporosis for SD patients increased with comorbidity.

In the nonapnea SD cohort, the adjusted HR was also significantly higher in women than in men (HR = 3.69, 95% CI = 3.51–3.88). The age-specific HR was also the highest in patients aged >64 years (HR = 31.2, 95% CI = 27.0–36.0), followed by those aged 40–64 years (HR = 13.3, 95% CI = 11.6–15.4) (Table 2).

Table 3 shows that the incidence of osteoporosis was much greater in patients without fracture than patients with pathologic

fracture. Compared with the non-SD cohort, the apnea SD cohort was found to be associated with an increased risk of osteoporosis without fracture (HR = 3.37, 95% CI = 2.69–4.21). The nonapnea SD cohort exhibited an increased risk of osteoporosis without fracture for all types of nonapnea SD, including insomnia (HR = 2.55, 95% CI = 2.41–2.70), sleep disturbance (HR = 2.91, 95% CI = 2.75–3.08), and others (HR = 2.97, 95% CI = 2.78–3.18).

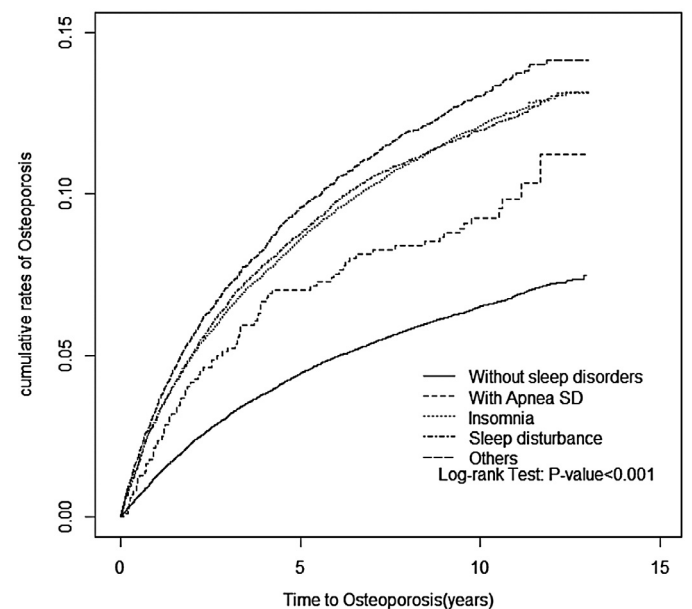


Fig. 1. Kaplan–Meier method determined cumulative incidence of osteoporosis compared between sleep disorder cohorts and comparisons without sleep disorder.

Table 2

Comparisons of incidence densities and hazard ratio of osteoporosis in study cohorts.

	Control		Apnea SD		IRR* (95% CI)	Adjusted HR† (95% CI)	Non-apnea SD		IRR* (95% CI)	Adjusted HR† (95% CI)
	Case	Rate#	Case	Rate#			Case	Rate#		
All	5469	6.77	80	9.97	1.47(1.26, 1.72)***	2.98(2.36, 3.74)***	5222	13.3	1.96(1.91, 2.02)***	2.76(2.64, 2.88)***
Gender										
Female	4557	9.24	56	22.1	2.39(1.93, 2.95)***	4.00(3.72, 4.29)***	4236	17.7	1.92(1.84, 1.99)***	3.69(3.51, 3.88)***
Men	912	2.90	24	4.38	1.51(1.24, 1.85)***	1(Reference)	986	6.43	2.22(2.11, 2.34)***	1(Reference)
Age										
≤39	78	0.33	1	0.39	1.14(0.75, 1.72)	1(Reference)	122	1.02	3.05(2.84, 3.30)***	1(Reference)
40–64	2643	6.24	42	9.59	1.54(1.24, 1.91)***	16.1(12.8, 20.1)***	2694	13.6	2.18(2.09, 2.28)***	13.3(11.6, 15.4)***
>64	2748	18.2	37	36.2	1.99(1.49, 2.67)***	42.0(33.5, 52.7)***	2406	31.9	1.76(1.67, 1.86)***	31.2(27.0, 36.0)***
Number of comorbidities										
0	1959	3.66	10	3.47	0.95(0.66, 1.35)	1(Reference)	896	6.07	1.66(1.58, 1.74)***	1(Reference)
1	1597	10.3	20	9.55	0.93(0.65, 1.34)	1.82(1.70, 1.95)***	1405	12.5	1.22(1.14, 1.29)***	1.68(1.59, 1.77)***
2	1045	14.6	21	13.4	0.91(0.62, 1.34)	2.07(1.92, 2.25)***	1396	19.3	1.32(1.22, 1.43)***	1.96(1.85, 2.08)***
≥3	868	19.0	29	19.6	1.04(0.74, 1.46)	2.38(2.19, 2.60)***	1525	25.4	1.34(1.23, 1.45)***	2.29(2.15, 2.43)***

Rate#, incidence rate, per 1,000 person-years; IRR*, incidence rate ratio, per 10,000 person-years; Adjusted HR†, multivariable analysis including age, sex, co-morbidities of diabetes, hypertension, hyperlipidemia, CKD, stroke, COPD, cancer, anxiety and depression and medication of benzodiazepine and zolpidem.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

4. Discussion

In Taiwan, the relationship between SD and osteoporosis has not been well investigated previously. In this 12-year retrospective follow-up study, we found a 144% higher osteoporosis incidence in the SD cohort than in comparisons incorporating major comorbidities. The osteoporosis risk is much greater in women than in men and in the elderly. The higher prevalence of comorbidities in SD patients could also contribute to the elevated osteoporosis risk. Our finding is consistent with the Norwegian study, which suggested that insomnia is a risk factor associated with several disorders, including osteoporosis [12]. Another important finding in our study is that SD patients without apnea have a higher osteoporosis incidence than those with apnea, with majority of patients without fracture.

Several risk factors for insomnia have been identified. Female sex, advanced age, and depression are consistent factors associated with higher insomnia prevalence [12]. Our data showed that 49.1% of SD cases were 40–64 years old and 60.7% were women. Most of the women have nonapnea SD. But, apnea SD was near two-fold more prevalent in men than in women. The osteoporosis risk was thus much greater in women than in men and it increased with age. In Western societies, the prevalence of obstructive sleep apnea

is common, affecting approximately 2% of the women population and 4% of the men [13]. In New Zealand, the prevalence of obstructive sleep apnea is higher among men [14].

Sex-related differences in osteoporosis have been widely reported. Women are at a greater risk of developing osteoporosis than men [20]. Women have lower bone marrow density and lose bone mass more quickly than men do as they age [20]. An American study showed that osteoporosis and low bone mass is more prevalent among women than among men, and this increased with age [21]. Similar findings have been reported for Asians in South Korea, China, and Taiwan [22–25]. The trabecular elements loss increases significantly in women with age [25].

The number of medical conditions increases with age such as arthritis, depression, and frequent need to urinate. These health conditions may cause fragmented sleep, and are associated with osteoporosis, particularly in women [26]. A recent Chinese study revealed that short sleep duration has a close association with lower bone marrow density, which led to lumbar degenerative scoliosis [27]. Our data showed that SD patients without apnea were older than those with apnea. This could explain why nonapnea patients have a higher osteoporosis incidence compared with apnea patients. Older nonapnea patients may also have a higher risk of death; the HRs would not reflect the difference in incidence.

Table 3

Comparisons of incidence and hazard ratios of osteoporosis with and without fracture by subtypes of sleep disorders.

Variables	N	Event	Rate#	IRR* (95% CI)	Adjusted HR† (95% CI)
Osteoporosis without fracture					
Non-SD	89,380	5,422	6.71	1(Reference)	1(Reference)
Apnea SD	846	80	9.97	1.50(1.20, 1.87)***	3.37(2.69, 4.21)***
Non-apnea SD					
Insomnia	18,127	2,087	13.1	1.93(1.83, 2.03)***	2.55(2.41, 2.70)***
Sleep disturbance	15,695	1,851	12.7	1.91(1.81, 2.01)***	2.91(2.75, 3.08)***
Others	10,022	1,250	14.3	2.10(1.98, 2.23)***	2.97(2.78, 3.18)***
Osteoporosis with pathologic fracture					
Non-SD	89,380	47	0.06	1(Reference)	1(Reference)
Apnea SD	846	0	0.00	–	–
Non-apnea SD					
Insomnia	18,127	14	0.09	1.53(0.84, 2.78)	1.35(0.69, 2.67)
Sleep disturbance	15,695	11	0.08	1.27(0.66, 2.45)	1.41(0.68, 2.91)
Others	10,022	9	0.10	1.79(0.88, 3.65)	1.77(0.81, 3.89)

Rate#, incidence rate, per 1,000 person-years; IRR*, incidence rate ratio; Adjusted HR†, multivariable analysis including age, sex, co-morbidities of diabetes, hypertension, hyperlipidemia, CKD, stroke, COPD, cancer, anxiety and depression and medication of benzodiazepine and zolpidem. ICD-9-CM: Osteoporosis without fracture: 733.0; Osteoporosis with pathologic fracture: 733.1; Apnea SD: 780.51, 780.53 and 780.57; Insomnia: 780.52; Sleep disturbance: 780.5 (excluded 780.51, 780.53 and 780.57); Others: 307.4, 780.50, 780.54–780.56, 780.58–780.59.

* $P < 0.05$; $P < 0.01$; *** $P < 0.001$.

Some medications may affect the bone marrow density. Patients on long-term conventional antipsychotic medication to treat schizophrenia experience increases in serum prolactin, which may be associated with osteoporosis [28]. In long term hypertension treatment, the bone marrow density in patients taking beta blockers is better than those taking calcium channel blockers [29]. In this study, SD patients are more likely to take benzodiazepine or zolpidem, and have higher osteoporosis incidence than comparisons (data not shown).

Other medical conditions associated with insomnia merit specific attention [13,15]. Sleep disorders play important roles in psychiatric symptoms and disorders [4]. Chronic illnesses are more prevalent in patients with SD than in those without SD. People with heart disease, cancer, high blood pressure, neurologic disease, breathing problems, urinary problems, diabetes, chronic pain, and gastrointestinal problems are more likely to have insomnia than those without these medical problems [16]. A German community survey found a moderate association between most anxiety disorders and sleep disturbance in the general population [30]. The Great Smoky Mountains Study in the United States also found that children and adolescents with sleep problems are more prevalent with psychiatric disorders [31]. Insomnia patients are usually treated with sedative medication and/or sleep hygiene advice [32]. The choice of the medication is benzodiazepine receptor agonist, such as zolpidem or benzodiazepine. For patients with obstructive sleep apnea, CPAP (continuous positive airway pressure) could be the choice [32].

Sleep insufficiency can increase the risk of cardiovascular disease, type 2 diabetes mellitus, obesity, cancer, and depression [4]. Patients with these comorbidities are at increased risk of osteoporosis [33,34]. Our study demonstrated similar findings. These comorbidities have an additive effect on the osteoporosis risk.

Studies have associated hypoxia, inflammatory cytokines, and increased oxidative stress with bone cell function [10,35]. Tomiyama et al. found that hypoxia constitutes an important pathophysiological change associated with obstructive sleep apnea. Bone cell function and other hypoxia-related diseases such as chronic respiratory disorders are thus affected, increasing the risk of osteopenia [10].

Sivertsen et al. found that patients with insomnia and other sleep disorders experienced chronic pain symptoms associating with fibromyalgia, osteoporosis, and musculoskeletal disorders [36]. An animal study shows that the amounts of osteoid diminished substantially in sleep-restricted rats, leading to a considerable decrease in osteoblast number and activity [37]. Bone marrow density in the femur was decreased as well in sleep-restricted rats [37]. Glucocorticoids are known to suppress bone formation, reduce bone strength and bone quality, and increase marrow adiposity, which may contribute to low bone mass [38,39]. Therefore, although both cohorts can lead to osteoporosis, the involved mechanisms seem to vary.

The strength of our study is the use of population-based data, highly representative of the general population. However, few limitations in this study must be considered. First, the insurance data do not provide information on laboratory examinations and lifestyle such as smoking and drinking, and family history of systemic diseases. We were unable to control these factors in measuring the osteoporosis risk. However, women in Taiwan rarely drink and smoke. Our risk estimations are likely reliable. Furthermore, the data regarding sleep disorders and osteoporosis diagnoses were reliable. Second, information on body weight was not available in the insurance claims data. We were unable to control the association between body weight and SD, and osteoporosis risk. Instead, our covariates included hypertension, diabetes, and hyperlipidemia. These three factors are associated with body weight. Third, this study is a retrospective cohort study, which may involve some potential biases derived from unknown confounding variables not adjusted. This study has included medications and several comorbidities in the data analysis. The risk of osteoporosis changes little for subjects with three or more comorbidities.

In conclusion, our findings suggest that patients with apnea SD or nonapnea SD exhibit higher risks of developing osteoporosis than comparisons with no SD, particularly among the elderly and those with more comorbidities. Women with SD should be cautious of osteoporosis risks to prevent subsequent fracture.

Conflict of interest

The authors have declared that no competing interests exist.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <http://dx.doi.org/10.1016/j.sleep.2014.07.005>.

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